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EXAMINER	
MEHTA, ASHWIN D	

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1638	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/521,288	FLASINSKI, STANISLAW	
	Examiner	Art Unit	
	Ashwin Mehta	1638	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *21 July 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,6-11,14,24,29 and 34* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,6-11,14,24,29 and 34* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *14 January 2005* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. The amendment filed July 21, 2008 was entered.

2. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

3. The amendment to the priority statement on page 1 of the specification, to correctly recite U.S. provisional application 60/396,665, is acknowledged.

4. The objections to claims 6-9, 14, 16-18, 23, and 24 are withdrawn in light of the claim cancellations or amendment.

5. The rejection of claims 16-18, 23, and 24 under 35 U.S.C. 101 is withdrawn in light of the claim cancellations or amendment.

6. The rejection of claims 1-5, 10-13, 16-18, 23, and 29-31 under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement, is withdrawn in light of the claim amendments.

7. The rejection of claims 1-4, 10, 11, 16, 23, and 29 under 35 U.S.C. 102(b) is withdrawn in light of the claim amendments.

8. The rejection of claims 16 and 23 under 35 U.S.C. 102(b) is moot in light of their cancellation.

9. The rejection of claims 16, 17, and 23 under 35 U.S.C. 102(b) is moot in light of their cancellation.

10. The rejection of claims 1-5, 10-13, 16, 23, and 29-32 under 35 U.S.C. 103(a) is withdrawn in light of the claim amendments or cancellations.

Claim Rejections - 35 USC § 112

11. Claims 1 and 29 remain and claim 34 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention, for the reasons of record stated in the Office action mailed March 18, 2008. Applicant traverses in the papers filed July 21, 2008. Applicant's arguments were fully considered but were not fully persuasive.

Claims 1 and 10, and those dependent thereon, were rejected because the recitation, "substantially identical protein" rendered the claims indefinite. The amendment to claims 1 and 10 obviates this aspect of the rejection.

The indefinite issue regarding claims 1 and 29 is maintained, and is applied to new claim 34. Applicants argue that the claims now recite that "the expression of the artificial and known polynucleotides is not silenced" and that this is supposedly consistent with the preamble

(response, page 7, 3rd full paragraph). The claims in line 1 indicate that they are directed to methods to reduce transgene silencing. However, there is no indication in the claims that such transgene silencing exists when the method is applied. The claims do not indicate that the known or other polynucleotide was post-transcriptionally silenced before application of the method. How can transgene silencing be reduced if it did not exist? The rejection is maintained.

12. Claim 1 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The recitation, "an artificial polynucleotide that is divergent from a known polynucleotide" renders the claim indefinite. It is unclear what is encompassed by "divergent". The claim indicates that the polypeptides encoded by SEQ ID NO: 18 and the known polynucleotide are at least 98% identical. However, this does not define "divergent" as used in the claim.

13. Claims 1, 8-11, 14, 29, and 34 are rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential elements, such omission amounting to a gap between the elements. See MPEP § 2172.01. The omitted elements are: a nucleotide sequence encoding a chloroplast target peptide fused to SEQ ID NO: 18 and to the "known" or other polynucleotide. The specification teaches that to express CP4EPSPS to confer glyphosate tolerance in plants, a chloroplast transit peptide is necessarily fused to the CP4EPSPS coding sequence to target enzyme accumulation in chloroplasts (page 64, lines 17-19). The claims do not mention

glyphosate tolerance, however the specification teaches that this is the purpose of expressing this enzyme in plants.

14. Claims 1, 8-11, 14, 29, and 34 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement because the specification, while being enabling for the claimed methods, plant cells and plants wherein the artificial polynucleotide of SEQ ID NO: 18, the known or other polynucleotide is SEQ ID NO: 16 and both encode SEQ ID NO: 15, and wherein a nucleotide sequence encoding a chloroplast transit peptide is operably linked to said polynucleotides, does not reasonably provide enablement for the claimed methods, plant cells or plants wherein the artificial and known polynucleotides encode proteins that differ by as much as 2%; and do not comprise a sequence encoding a chloroplast transit peptide. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims. This rejection replaces the scope of enablement rejection of the Office action mailed March 18, 2008. Applicant traverses that rejection in the papers filed July 21, 2008. Applicant's arguments as they apply to the instant rejection were fully considered but were not found persuasive.

Claim 1 is broadly drawn towards a method to reduce transgene silencing in transgenic plants, comprising the steps of a) obtaining a DNA construct comprising an artificial polynucleotide that is divergent from a known polynucleotide, wherein the known and artificial polynucleotides encode polypeptides that are at least 98% identical; b) transforming the construct into a plant cell, and c) regenerating a fertile transgenic plant from the plant cell, wherein the

artificial polynucleotide is SEQ ID NO: 18, and wherein said plant comprises both said artificial polynucleotide and the known polynucleotide, and wherein the expression of said artificial and said known polynucleotides is not silenced. Claim 8 is directed to a plant cell, plant, or progeny thereof comprising a DNA construct comprising a promoter operably linked to SEQ ID NO: 18. Claim 10 is broadly drawn to any plant cell comprising at least two polynucleotides, wherein said two polynucleotides encode polypeptides that are at least 98% identical and at least one of the polynucleotides is SEQ ID NO: 18. Claim 11 is drawn towards a plant or progeny thereof comprising the cell of claim 10. Claim 29 is broadly drawn towards a method of reducing transgene silencing in transgenic plants comprising (a) obtaining the cell of claim 10 and (b) regenerating said cell into a fertile transgenic plant.

The specification discusses how several artificial polynucleotides encoding EPSP synthases, described in the sequence listing, were constructed, all of which were modified from a polynucleotide known to encode an EPSP synthase. Some EPSP synthases encoded by the artificial polynucleotides differ slightly from that encoded by the known or original EPSPS-encoding polynucleotide. However, the claims are not limited to artificial and known polynucleotides encoding EPSP synthases, but broadly encompass any type of proteins. The specification does not enable constructing artificial polynucleotides encoding proteins that differ in sequence identity from that encoded by the known or original polynucleotide, except for EPSPS. No guidance is provided regarding what kind of amino acid changes can be sustained by any given protein without affecting its functional activity. The example of EPSPS is not applicable to any other type of protein, as other proteins of course have differing structures and mechanisms of action. The type of number of changes any protein can sustain, if at all, cannot

be extrapolated to any other protein. In the absence of further guidance, undue experimentation would be required for one skilled in the art to determine how any given protein may be changed without affecting its functional activity.

Applicants argue that in view of the current amendments to claims 1, 10, and 29 to pertain to SEQ ID NO: 18, this rejection is rendered moot (response, page 8). SEQ ID NO: 18 was produced by back translating SEQ ID NO: 15 with Zea mays codon usage (Example 4). SEQ ID NO: 15 is the Agrobacterium tumefaciens EPSPS protein, and its native polynucleotide sequence is in SEQ ID NO: 16. The polypeptide encoded by SEQ ID NO: 18 is the sequence of SEQ ID NO: 15. However, while the claims have been amended to limit the artificial polynucleotide to encode SEQ ID NO: 18, they do not limit the identity of the "known" or other polynucleotide(s) encoding a protein having 98% identity to SEQ ID NO: 15. The claims do not recite that the polypeptide encoded by the "known" or other polynucleotide is SEQ ID NO: 15. As written, the polypeptide encoded by the known or other polynucleotide can have any function. The specification does not teach other polynucleotides encoding polypeptides that one skilled in the art can compare with the polypeptide encoded by SEQ ID NO: 18, to determine percent identity and retention of function.

Further, even in the case of EPSPS, the specification does not teach changes that can be made to SEQ ID NO: 18 such that the encoded protein differs from that encoded by another polynucleotide, known or otherwise, by as much as 2%. Example 4 in the specification discusses the construction of SEQ ID NO: 18. The amino acid sequence of SEQ ID NO: 15, which is the A. tumefaciens strain CP4 EPSP synthase, was back translated using Zea mays codons. The specification does not state what the amino acid sequence is that is encoded by SEQ ID NO: 18.

However, one reading frame of SEQ ID NO: 18 encodes the same amino acid sequence as in SEQ ID NO: 15. The other two reading frames of SEQ ID NO: 18 encode much shorter peptides. Therefore, the only "known" polynucleotide that encodes a polypeptide that shares at least 98% identity with the polypeptide encoded by SEQ ID NO: 18, is SEQ ID NO: 16, the native A. tumefaciens CP4 EPSPS coding sequence. Further, there is no difference in sequence identity between the encoded polypeptides. The specification does not teach any polypeptides, and the polynucleotides encoding them, that differ from SEQ ID NO: 15 by as much as 2%. SEQ ID NO: 15 is 455 amino acids in length. A difference of 2% amounts to 9.1 amino acids. However, the specification does not teach any modified EPSPS that differs from the original by this amount. Example 1 indicates that 2 amino acids were substituted to provide a modified rice EPSPS, and Example 3 indicates that 3 amino acids changes were made to produced a modified soybean EPSPS. However, these amounted to changes of percent identity of 0.39% and 0.57% from the original sequences, respectively. The specification does not provide any guidance regarding changes that can be made to the amino acid sequence encoded by SEQ ID NO: 18 such that 10 amino acids may be changed without affecting functional activity. Undue experimentation would be required by one skilled in the art to determine what other amino acid changes can be made without affecting functional activity.

Further, while claims 1, 29, and 34 are drawn to methods to reduce gene silencing, the claims still allow for SEQ ID NO: 18 and the "known" or other polynucleotide to share enough nucleotide sequence identity to trigger co-suppression. While claim 1 states that the artificial polynucleotide is divergent from a known polynucleotide, it is unclear how different the two sequences are, especially since they can encode the same amino acid sequence. Claims 29 and

34 do not mention anything regarding the level of identity shared between SEQ ID NO: 18 and the other nucleotide sequence. The specification at page 2 asserts that gene silencing may occur when heterologous genes are introduced that are too similar to an endogenous gene DNA sequence in the plant. Thomas et al. (Plant J., 2001, Vol. 25, pages 417-725) also assert that post-transcriptional gene silencing is based on homology-dependent degradation of RNA in the cytoplasm (page 417). As written, the claims embrace the non-enabled embodiment that allows SEQ ID NO: 18 to still share enough sequence identity with the known or other polynucleotide, such that silencing may not be avoided.

Furthermore, the specification teaches that to express CP4EPSPS to confer glyphosate tolerance in plants, a chloroplast transit peptide is necessarily fused to the CP4EPSPS coding sequence to target enzyme accumulation in chloroplasts (page 64, lines 17-19). However, the claims do not include a nucleotide sequence encoding a chloroplast transit peptide fused to SEQ ID NO: 18 or the "known polynucleotide". As such, even if the polypeptides encoded by the polynucleotides are EPSPS proteins, they will not confer glyphosate tolerance to the host plants or cells. While the claims do not recite that such tolerance is to be conferred, the specification does not teach how else one skilled in the art would use such host plants or cells. It appears that the fusion of a chloroplast transit peptide-encoding nucleotide sequence to the SEQ ID NO: 18 and the "known polynucleotide" is essential to the invention, but is not recited in the claims. As such, the claims are not enabled. See MPEP 2164.0(c) and 2171.01.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

15. Claims 1, 6-11, 14, 24, 29, and 34 are rejected under 35 U.S.C. 103(a) as being unpatentable over Drake et al. (WO 97/46690) in combination with Barry et al. (U.S. Patent No. 5633435, issued May 27, 1997), and Murray et al. (Nucl. Acids Res. 1989, Vol. 17, pages 477-498).

Claim 1 is broadly drawn towards a method to reduce transgene silencing in transgenic plants, comprising the steps of a) obtaining a DNA construct comprising an artificial polynucleotide that is divergent from a known polynucleotide, wherein the known and artificial polynucleotides encode polypeptides that are at least 98% identical; b) transforming the construct into a plant cell, and c) regenerating a fertile transgenic plant from the plant cell, wherein the artificial polynucleotide is SEQ ID NO: 18, and wherein said plant comprises both said artificial polynucleotide and the known polynucleotide, and wherein the expression of said artificial and said known polynucleotides is not silenced. Claim 6 is drawn to an artificial polynucleotide comprising SEQ ID NO: 18. Claims 7-9 are directed to a DNA construct, or plant cell, plant, or progeny thereof comprising a DNA construct comprising a promoter operably linked to SEQ ID NO: 18. Claim 10 is broadly drawn to any plant cell comprising at least two polynucleotides, wherein said two polynucleotides encode polypeptides that are at least 98% identical and at least

one of the polynucleotides is SEQ ID NO: 18. Claim 11 is drawn towards a plant or progeny thereof comprising the cell of claim 10. Claim 24 is drawn to a DNA detection kit comprising at least one DNA molecule selected from SEQ ID NO: 26 or 27; Claim 29 is broadly drawn towards a method of reducing transgene silencing in transgenic plants comprising (a) obtaining the cell of claim 10 and (b) regenerating said cell into a fertile transgenic plant.

Drake et al. teach the tomato nucleotide sequence, TOM5, encoding the phytoene synthase gene, and a modified form of that nucleotide sequence, MTOM5 (also referred to as CGS48), which encodes the same protein. Drake et al. also teach a method to enhance expression of a selected protein in a plant having a gene that produces that protein, by transforming it with a nucleotide sequence that differs from that of the gene already present in the plant. Drake et al. assert that co-suppression occurs when plant recombinant genes are introduced into plants that already contain a gene with similar nucleotide sequence, and that co-suppression is obviated or mitigated by inserting and expressing in a plant a nucleotide sequence encoding an RNA that is different from that already present in the plant but encodes the same protein. Drake et al. provide directions for synthesizing the nucleotide sequence encoding the selected protein which differs from the natural encoding sequence. MTOM5 was inserted into a plant expression vector, operably linked to the CaMV 35S promoter, and transformed into tomato stem segments. Transformed plants were regenerated from the transformed tissue. Northern blot analysis confirmed that the MTOM5 gene sequence was expressed. With a normal GTOM5 construct, 28% of transgenic plants display a co-suppressed phenotype. All the plants carrying the modified MTOM5 construct had red fruit, demonstrating that no suppression of

phytoene desaturase synthesis occurred in any of them. The transformed plants were fertile, as some were selfed to produce progeny (pages 2-4, 7-13, claims).

Drake et al. do not disclose EPSPS-encoding genes.

Barry et al. teach the nucleotide sequence encoding the Agrobacterium tumefaciens strain CP4 EPSPS protein. Barry et al. also assert that this EPSPS gene contains sequences that could be inimical to high expression in plants, and that improvements in codon usage, elimination of potential polyadenylation sequences, and disruption of stretches of G's and C's could result in higher expression in plants. Barry et al. also teach expression of this EPSPS in transgenic plants, with an operably linked chloroplast target peptide. Transgenic plants showed glyphosate-resistance (SEQ ID NO: 2; Fig. 3; col. 27, line 55 to col. 28, line 5; Example 1). Instant SEQ ID NO: 16 also presents the A. tumefaciens strain CP4 nucleotide sequence encoding EPSPS.

Murray et al. teach codon usage in maize (Table 4).

It would have been obvious and within the scope of one of ordinary skill in the art to use the method of enhancing expression of a selected protein of Drake et al., to enhance expression of any desired protein, including one that provides the desirable trait of glyphosate resistance. Drake et al. assert that co-suppression occurs when plant recombinant genes are introduced into plants that already contain a gene with similar nucleotide sequence, and that co-suppression is obviated or mitigated by inserting and expressing in a plant a nucleotide sequence encoding an RNA that is different from that already present in the plant. It would have been obvious to use the method of Drake et al. to produce an RNA that differs from an EPSPS-encoding nucleotide sequence of Barry et al, including the A. tumefaciens strain CP4-encoded EPSPS, using the

desired codon usage based on the desired host plant. For example, for expression in monocot plants including corn, it would have been obvious to use maize preferred codons taught by Murray et al. Such a modification would have yielded the sequence in instant SEQ ID NO: 18, and encode the same protein. It would have been obvious to introduce and express that modified nucleotide sequence in the transgenic plants already expressing the unmodified EPSPS (that is, before modification by the method taught by Drake et al.), in order to achieve enhanced expression of the encoded EPSPS. Any subsequence of the modified nucleotide sequence, including those of SEQ ID NO: 26 or 27, could be used in hybridization or PCR experiments to verify the presence of the modified nucleotide sequence in the transgenic plants. One would have been motivated to achieve enhanced expression of EPSPS in plants, to further increase herbicide resistance of the host plant.

Contact Information

Any inquiry concerning this or earlier communications from the Examiner should be directed to Ashwin Mehta, whose telephone number is 571-272-0803. The Examiner can normally be reached from 8:00 A.M to 5:30 P.M. If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Anne Marie Grunberg, can be reached at 571-272-0975. The fax phone numbers for the organization where this application or proceeding is assigned are 571-273-8300. Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished

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October 24, 2008

/Ashwin Mehta/
Primary Examiner, Art Unit 1638